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Diagnostic Criteria for Sepsis

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Abstract: Sepsis is one of the few complications of infectious diseases that is still considered one of the most critical and life-threatening. The frequency of sepsis is growing every year, which is facilitated by increasing resistance to antimicrobial drugs, the widespread introduction of new medical technologies, the expansion of indications for cytostatic and immunosuppressive therapy, the development of transplantology and prosthetics, as well as the HIV pandemic. This article describes and summarizes methods for the early diagnosis of sepsis based on a literature review of publications from different countries.

Keywords: sepsis, septicemia, sepsis markers, septic shock, biomarkers.

Introduction

Sepsis remains a global public health problem that has not lost its relevance throughout the entire period of study of this pathological condition [2, 6, 7, 9, 13, 22]. The incidence of sepsis in the world is growing by about 1.5% annually, which is facilitated by increasing resistance to antimicrobial drugs, the widespread introduction of new medical technologies, the expansion of indications for cytostatic and immunosuppressive therapy, the development of transplantation and prosthetics, as well as the HIV pandemic [22] . Significant success has been achieved in understanding the general biological mechanisms of the body's response to bacterial aggression and the alteration associated with it [8]. Sepsis is based on the formation of a generalized inflammation reaction initiated by an infectious agent, in response to which an uncontrolled release of endogenous inflammatory mediators occurs, an insufficiency of mechanisms is formed that limits their damaging effect, which ultimately causes organ system disorders [22, 23]. Despite significant advances in the study of the biological concept of systemic inflammation, it is still premature to talk about significant progress in the timely diagnosis and treatment of sepsis [4, 5, 9, 13, 14, 16]. In addition, discussions about the definition, diagnosis and treatment of sepsis, severe sepsis (TS) and septic shock (SS) do not stop in the world. On a global scale, the development of protocols and forms for the registration and treatment of patients with sepsis was impossible without the unification of terminology, classification and diagnostic principles, which was carried out 25 years ago in the framework of the Conciliation Conference of the American Societies of Pulmonologists and Critical Medicine Specialists [11]. Within the framework of this and subsequent conciliation conferences, until recently, it was proposed to base the diagnosis of a generalized infectious process on the universal criteria for systemic inflammatory response syndrome (SIRS), sepsis, TS and SS, as well as the fact of the presence of an infectious agent [11, 13]. Further development of the doctrine of sepsis is associated with the introduction of the principles of evidence-based medicine into clinical practice. It is on these foundations that the recommendations for the treatment of sepsis, created within the framework of the international program "Movement for effective treatment of sepsis - 2012" are based. (Surviving Sepsis Campaign "SSC-2012"), reflecting the interdisciplinary experience of experts from more than 30 associations [13]. For the convenience of understanding the

provisions of SSC-2012, uniform principles were adopted, according to which the degree of recommendations should be understood as A - high, B - moderate, C - low, D - very low. Additionally, the weight value of recommendations was determined: as strong, i.e., recommended for use (1), and weak, i.e., possible recommendation (2).

Main part. To verify sepsis, it is recommended to routinely examine patients with organ failure for the presence of infection in order to timely detect TS and implement appropriate early therapy (1C). To improve bacteriological verification of the diagnosis, all samples for microbiological studies should be taken immediately upon admission of the patient, unless this is associated with a significant delay in the start of antibiotic therapy (ABT) (more than 45 min) (1C). It is preferable to carry out 2-3-time blood sampling with an interval of 30-60 minutes. At least 2 blood samples should be taken for the study before the start of ABT, with 1 from the percutaneous method, and the other from a vascular catheter placed less than 48 hours ago (1C), while each material should be placed in a container with aerobic and anaerobic environment. Classical laboratory markers of the inflammatory process have low specificity and are not reliable enough for early and accurate diagnosis of sepsis. Modern microbiological studies are highly specific, but their overall sensitivity does not exceed 25–45% [8]. Considering that mortality in sepsis is largely due to its late diagnosis and ineffective monitoring of ongoing treatment, the search for reliable markers of infectious SIRS is of particular interest. In most clinical situations, it is not possible to convincingly answer the question: what is the nature of SSVR - a reflection of physiological processes of an aseptic nature or a manifestation of an infection? However, the choice of effective treatment tactics depends on the solution of this issue. First of all, this concerns the latent (not obvious) course of sepsis. Thus, according to the results of a multicenter study by V. Liu et al . from Oakland (USA) [19], in a multi-million sample of patients, it was found that the majority of deaths occurred in the clinically latent course of sepsis, when the indicators of the timeliness and adequacy of the treatment program were significantly inferior to those in the cohort of initially severe patients. Thus, the conclusion suggests itself about increased attention to patients with initially mild sepsis, which is an additional reserve for reducing mortality. In the recommendations of "SSC-2012" [13], in a more accentuated form, an attempt was made to expand the definition of sepsis in relation to all age groups. Indications of the diagnostic significance of deviations in heart rate and systolic blood pressure (by two square deviations from the age norm), specification of the concept of tachypnea and a decrease in capillary filling time make it possible to more accurately diagnose SSVR in children as well [5]. That is why in the process of diagnosis, especially with an unidentified infectious focus, the SSC-2012 experts recommend focusing on the extended clinical and laboratory criteria for sepsis (RCS) [13] (table). As an illustration of the validity of the implementation and testing of RCS, the results of a study by A. Whippy et al . [26], according to which the authors managed to increase the effectiveness of targeted screening for sepsis from 35.7 to 119.4 per 1000 hospitalizations, using an elevated blood lactate level as an additional test in a high- risk group of patients. The frequency of diagnosing sepsis with this approach increased from 27 to 97%, and the implementation of the principle of early targeted therapy made it possible to achieve an increase in the proportion of patients with a prognostically favorable reduced lactate level from 52 to 92% within a 6-hour treatment period. As a result of the long experience in using the ACCP / SCCM criteria, more and more grounds began to appear for a critical look at their clinical appropriateness, while the opinion began to dominate that the primary diagnosis of sepsis remains one of the most difficult tasks of modern sepsisology . A growing number of supporters of the opinion that the term "sepsis" should be used only in situations where the systemic inflammatory response is clinically pronounced [3, 6, 7, 9, 10, 16]. This means that sepsis should only manifest itself in the following forms:

a) TS, understood as sepsis in combination with organ damage, hypoperfusion (including lactic acidosis, oliguria and acute impairment of consciousness) and hypotension;

b) SS, understood as sepsis in combination with hypoperfusion injury and persistent hypotension not relieved by adequate volumetric replacement;

c) multiple organ failure syndrome (MODS), which appears to be the final stage of an acute systemic inflammatory response.

According to A. B. Larichev [3], based on the experience of treating patients with purulent surgical infection of soft tissues, the presence of SSVR and a proven focus of infection is too favorable a clinical situation to consider it as sepsis, since at the modern level of surgery it is quite achievable to the maximum the optimistic result is 100% recovery, which is impossible to imagine if one follows the logic of stratifying the criteria for generalized ACCP/SCCM infection. Thus, the elevation of SSVR to the rank of a classification criterion for sepsis, in his opinion, is not required, and this term itself should not be included in the diagnosis. A similar conclusion, but on the basis of a different argumentation, came I. V. Nekhaev from the Russian Cancer Research Center. N. N. Blokhin of the Russian Academy of Medical Sciences [6], who, using the model of patients who underwent thoracoabdominal oncological operations, tested the algorithm for diagnosing sepsis, including: the presence of a focus of infection, the presence of 3 or 4 SSVR criteria, confirmed MODS (to formulate the diagnosis of "severe sepsis") or shock (for the formulation of the diagnosis of "septic shock"). A procalcitonin test was used to rule out the diagnosis of sepsis . Thus, sepsis in this category of patients, according to I. V. Nekhaev , should be stated either in the form of TS or in the form of SS, and the independent category "sepsis" has lost its clinical significance, to confirm the generalization of the infectious process is a more important and mandatory condition than SSVR is the presence of organ failure, manifested in the form of MODS or shock. In other clinical situations, according to the author, the development of the disease should be interpreted as a less severe infection, such as pneumonia, pyelonephritis or peritonitis, causing dysfunction of only the organ in which the infectious process is localized. A similar approach to the definition of sepsis was tested in generalized purulent peritonitis (PPP) by S. S. Maskin et al . [4]. According to it, the absence of sepsis in RGP was recognized as a situation when there was an intra-abdominal source of infection + 1–2 SSVR criteria + there were no signs of intestinal failure syndrome (IIS) stage II–III, of the manifestations of this syndrome, only a violation of the motor-evacuation function of the intestine can be present , there are also no manifestations of organ failure (SOFA=0). Diagnosis of abdominal sepsis was based on the following algorithm: a confirmed focus of infection + the presence of 3 or 4 criteria for SIRS + SCI stages II–III + the presence of criteria for failure of one organ (system) corresponding to a SOFA score of 3 points or less. The criteria for abdominal TS correspond to the situation when the presence of MODS, assessed on the SOFA scale of 4 points or more, is ascertained. Another example of an attempt to improve the diagnostic criteria for sepsis is the development of the previously proposed PIRO concept [12, 20]. The low specificity of the SSVR criteria was the reason for the development of additional approaches to the differential diagnosis of syndromes of infectious and non-infectious genesis. Depending on their effectiveness in solving specific clinical problems, any biological markers can be classified as diagnostic, prognostic, and monitoring [21]. The potential role of biomarkers in diagnosing infection in TS patients remains uncertain. Within the framework of SSC-2012, an international group of scientists, due to insufficient evidence, found no reason to recommend any of the biomarkers as a "diagnostic" one in sepsis.

Extended clinical and laboratory criteria for sepsis

Infection, suspected or confirmed, in combination with more than one of the following criteria	
General Criteria	1. Hyperthermia (temperature above 38.3 ºC) 2. Hypothermia (temperature below 36 ºC) 3. Heart rate greater than 90 per minute or greater than 2 standard deviations from the normal age range 4. Tachypnea , impaired consciousness 5. The need for infusion support (more than 20 ml / kg in 24 hours) 6. Hyperglycemia (more than 7.7 mmol / l) in the absence of diabetes mellitus
Criteria for inflammation	1. Leukocytosis more than 12×109/l, leukopenia less than 4×109/l 2. Shift towards immature forms (more than 10%) with a normal content of leukocytes 3. The content of C-reactive protein in blood plasma is more than 2 standard deviations from the norm 4. The content of procalcitonin in blood plasma is more than 2 standard deviations from the norm
Hemodynamic criteria	1. Arterial hypotension: BP syst . less than 90 mm Hg. Art., SBP less than 70 mm Hg. Art. or decrease in blood pressure syst . more than 40 mm Hg. Art. (in adults), or a decrease 2. Syst . BP is at least 2 standard deviations below normal for age 3. SvO2 saturation less than 70% 4. Cardiac index less than 3.5 l/(min m2)
Criteria for organ dysfunction	1. Arterial hypoxemia PaO2 /FiO2 less than 300 2. Acute oliguria less than 0.5 ml/(kg h) 3. An increase in plasma creatinine by more than 44 μmol / l (0.5 mg%) 4. Coagulation disorders: APTT over 60 s or INR over 1.5 5. Thrombocytopenia less than 100×109/l 6. Hyperbilirubinemia more than 70 mmol / l 7. Intestinal paresis (lack of bowel sounds)
Indicators of tissue hypoperfusion	1. Hyperlactatemia more than 1 mmol / l 2. Symptom of delayed filling of capillaries, marbling of the skin of the extremities

More specifically, this is formulated in relation to procalcitonin (PCT) - the international consensus does not recommend using the PCT level as a diagnostic tool for verifying TS. It is recommended to focus on low PCT or other biomarkers to stop empirical antibiotic therapy in the absence of foci of infection (2C), but not as evidence of infection, since the possibility of increased PCT in autoimmune diseases and after traumatic operations should be borne in mind. From the explanations to the SSC-2012 recommendations, it follows that the main diagnostic role of determining PCT is to exclude sepsis at its level below 0.5 ng / ml. At a diagnostic PCT level of more than 1.1 ng /ml, the sensitivity of the test is 97%, and the specificity is 78%, and at its level of more than 2 ng /ml, there is an increased likelihood of bacterial sepsis [9]. In comparison with other markers of SSVR, PCT is characterized by rapid induction under the influence of predominantly infectious stimuli, high stability in vitro and in vivo , wide concentration range, high specificity. The PCT induction period (about 6–12 h) is shorter than for C-reactive protein (CRP) and longer than for pro- inflammatory cytokines [8]. Over the past few years, there has been increased interest in studying a PCT

competitor in the diagnosis of sepsis, presepsin (PS) [1, 14, 24, 27]. To understand the mechanism of increased PS concentration in bacterial infection, it is necessary to highlight the role of several participants in the bacterial inflammation process, namely: bacterial endotoxins — lipopolysaccharide (LPS), macrophage receptor CD14 and its free soluble form CD14, and lipopolysaccharide -binding protein (LPB). After Y. Yaegashi et al . [27] found a previously unknown form of sCD14 in the blood of septic patients; subsequent studies found that a peptide fragment is cleaved from sCD14 under the action of circulating protease in the sCD14–LPS–LPB complex during a bacterial infection. As a result, a truncated form of sCD14 of 64 amino acid residues is formed, originally called the sCD14 subtype (subtype sCD14-ST) and then renamed PS [1]. PS is a protein, the concentration of which in the blood increases rapidly with the development of bacterial sepsis, i.e., with the maximum activity of phagocytosis. According to Y. Okamura et al . [24], PS demonstrated in patients with sepsis a discriminating ability that exceeded that for PCT and correlated with the APACHE II scale. According to the results of a multicenter study by S. Endo et al . [14], the clinical specificity of PS exceeded that of PCT. In particular, sensitivity to bacterial infection was 91.9% for PS, 88.9% for PCT, 88.9% for interleukin-6, and 35.4% for blood cultures . The frequency of false positive diagnoses was 12.5% for PS and 25% for PCT. The mean PS concentration in gram-positive sepsis was (2881±437) pg /ml with a sensitivity of 95.5%, and in gram-negative sepsis it was (2641±379) pg /ml and 77.7%. PS can serve as a new highly specific and highly a co-sensitive marker of sepsis, since it reflects its dynamics earlier and faster than other known markers [1]. Determining the level of PS is very effective for the early diagnosis of sepsis, its monitoring and prediction of adverse outcomes. The use of PS is also promising for scientific research aimed at elucidating the factors influencing phagocytosis and searching for appropriate drugs [1]. For differential diagnosis and monitoring of systemic inflammation and sepsis, the combined measurement of CRP, PCT, PS levels seems to be the most appropriate, which, of course, is not feasible in most domestic clinics due to financial reasons. At the same time, the dynamics of these markers, and not their absolute values, has the greatest clinical significance. M. G. Vershinina and N. B. Kukhtina [2] are supporters of using a combination of the following biomarkers for the diagnosis of sepsis : PCT, CRP, interleukin-6, LBP. Taking into account the improvement of methods of microbiological diagnostics of sepsis, attempts to increase the availability of the determination of various cytokines and endotoxin do not stop. In addition, hopes remain that non- cultural diagnostic methods such as polymerase chain reaction and mass spectroscopy will be useful in the diagnosis of sepsis in the future [18]. The most promising biomarkers of bacterial sepsis in adults should also include sTREM-1 (soluble Triggering Receptor expressed on Myeloid cells) is a soluble form of the trigger receptor expressed on monocytes [15], suPAR (soluble uro kinase-type Plasminogen Receptor) is a soluble, urokinase -type plasminogen receptor and proadrenomedullin (ProADM) [17]. The most important result of the two-year work of the working group led by M. Singer and CS Deutschman [25], positioning itself as "Sepsis-3", was the publication of the final article entitled "The third international consensus on the definition of sepsis and septic shock." The postulates set out in the final recommendations of the working group of 19 scientists contain the "revolutionary" nature of changes in understanding the definitions and categories of generalized infection. Without aiming to conduct a detailed analysis of this document, we note only the key provisions of the Sepsis-3 recommendations. Instead of such categories and concepts previously accepted for understanding sepsis, such as SIRS, sepsis, severe sepsis and septic shock, the Sepsis-3 recommendations recommend using the terms: “sepsis” (a condition previously defined as severe sepsis) and “septic shock ". Sepsis is defined by the working group as a life-threatening organ dysfunction resulting from dysregulation of the body's response to infection. The cardinal difference from the definition of sepsis, which has

dominated the world over the past 25 years, is that the unconditional priority of the mandatory presence of organ dysfunction in sepsis is recognized, and the SSVR criteria (2 or more) are recognized as useless for the definition of sepsis and reflect only the characteristics of the body's response to infection. Organ dysfunction can be defined as an acute change in total SOFA score of 2 or more due to infection, which in practice reflects a 10% increased risk of hospital mortality in the general population of patients with suspected infection. For screening patients with suspected sepsis who are not in the intensive care unit (ICU), a "sparing" model of the SOFA scale, or qSOFA (quick SOFA), has been proposed, which includes the following criteria:

a) altered consciousness (according to the Glasgow scale 13 points or less);

b) decrease in systolic blood pressure to 100 mm Hg. Art. and below;

c) an increase in the frequency of respiratory movements (RR) up to 22 in 1 min or more.

A complete SOFA score is recommended for screening for sepsis in ICU patients. Identification of patients with SS, according to "Sepsis-3", is proposed to be carried out on the basis of the clinical picture of sepsis against the background of adequate infusion therapy, an increase in blood lactate levels of more than 2 mmol / l, persistent hypotension requiring the introduction of vasopressors to maintain a SBP of 65 mm Hg. Art. and more.

Conclusions . Thus, sepsis, as a general biological and clinical problem, is a special area of medical knowledge and practice. Early diagnosis of sepsis in a significant proportion of cases is difficult due to the heterogeneity of the nature of the septic process and the fact that many of its clinical manifestations are not specific enough. The circumstance that the discrepancy between the clinical, pathological-morphological and legal statement of the diagnosis "sepsis" does not add much optimism to practitioners . The results and proposals of the latest international recommendations of the Sepsis-3 consensus are subject to careful analysis, discussion and clinical testing at the national level. The identification of patients who initially have the highest risk of generalization of infection is of paramount importance, since only early targeted therapy for severe sepsis and shock has a proven clinical effect, which is why today significant efforts of the entire medical community are focused on finding the most effective diagnostic markers of sepsis

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